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Identification of $bla_{OXA-51-23-58}$, bla_{VIM}, bla_{NDM}, and bla_{IMP} carbapenemase genes in *Acinetobacter baumannii* isolates from hospitalized patients

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Abstract

Objective The increase of multidrug-resistant (MDR) strains of *Acinetobacter baumannii* (*A. baumannii*), especially carbapenem-resistant strains, is challenging for treating infections. This study investigated the antibiotic resistance pattern and frequency of carbapenem resistance genes (oxacillinase and metallo-beta-lactamase) in *A. baumannii.*

Results In this study, 100 bacterial isolates were collected from clinical samples from different hospitals in Isfahan, central of Iran. Of 100 samples of bloodstream, urine, cerebrospinal fluid (CSF), wound, and trachea, 60 bacteria were identified as *A. baumannii*. The results showed that 100% of the selected isolates were resistant to cefotaxime, ceftazidime, ciprofloxacin, piperacillin-tazobactam, and meropenem. Based on the antibiotic resistance pattern, 25 isolates were chosen for PCR analysis targeting bla_{OXA-51}, bla_{OXA-23}, bla_{OXA-58}, bla_{NDM}, bla_{IMP}, and bla_{VIM} genes PCR results revealed that among the selected isolates, 15 (60.0%) harbored the bla_{OXA-23} gene, 23 (92.0%) contained the bla_{OXA-51} gene, and 1 (4.0%) isolate carried the bla_{NDM} gene. Based on MLST analysis, two colistin-resistant *Acinetobacter baumannii* isolates were categorized as ST2. The ST2 clone represents the predominant sequence type within the CC2 or international clone two. The results showed that the best antibiotic against isolates was colistin. bla_{OXA-51} and bla_{OXA-23} genes (oxacillinase genes) were dominant genes, but bla_{IMP} and bla_{OXA-58} were not local carbapenem resistant genes in Isfahan.

Keywords *Acinetobacter baumannii*, Carbapenem-resistant, Multidrug-resistant strains

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Introduction

Acinetobacter baumannii, a Gram-negative bacterium, recognized as a formidable nosocomial pathogen, posing a substantial burden on healthcare systems globally due to its propensity for antibiotic resistance [1]. In some regions, *A. baumannii* accounts for a significant proportion of healthcare-associated infections, including ventilator-associated pneumonia, bloodstream infections, urinary tract infections, and surgical site infections. Its ability to persist in the hospital environment, survive on surfaces via biofilm formation, and develop resistance to multiple antibiotics contributes to its prevalence and challenges in infection control [2, 3]. Among the key contributors to *A. baumannii* multidrug-resistant (MDR), various oxacillinase and metallo-β-lactamases gene encoding enzymes play a crucial role [4, 5]. These enzymes confer resistance by hydrolyzing β-lactam antibiotics, such as carbapenems, rendering them ineffective in treating A. baumannii infections [6, 7].

While *OXA*-type β-lactamases predominantly target carbapenems, *VIM*-type, *IMP*-type, and *NDM*-type metallo-β-lactamases exhibit broad-spectrum activity against various β-lactam antibiotics [8, 9].

A variety of methodologies exist to enhance our understanding of the geographical distribution of Acinetobacter, including Multilocus Sequence Typing (MLST) and Random Amplification of Polymorphic DNA (RAPD) [10, 11]. MLST serves as a robust tool for investigating the global epidemiology of *A. baumannii*, utilizing conserved regions from seven housekeeping genes [12]. Epidemiological research on clinical isolates of *Acinetobacter* across the globe has revealed significant genetic diversity, with most infections attributed to specific isolates. Additionally, studies conducted in Iran indicate that the majority of identified sequence types (STs) in the country fall under clonal complex 92, which is associated with ICL-2 [13].

The presence of metallo-β-lactamase genes in *A. baumannii* strains highlights the urgent need for effective infection control measures, antimicrobial stewardship programs, and the development of alternative treatment strategies to combat MDR infections caused by this opportunistic pathogen. In this study, we investigated the prevalence of carbapenem resistance genes (oxacillinase and metallo-beta-lactamase), including $bla_{\text{OXA-23}}$, $bla_{\text{OXA-51}}$, $bla_{\text{OXA-58}}$, bla_{VIM}, bla_{NDM}, and bla_{IMP}, and molecular characterization of colistin resistant isolates of *A. baumannii* isolated from hospitalized patients from different hospitals, Isfahan, Iran.

Methods and materials

Study Design and bacterial isolation

In this study, 100 samples of urine, cerebrospinal fluid (CSF), respiratory system, bloodstream, and wound (surgery or burns) from hospitalized patients in different wards of hospitals in Isfahan (two teaching hospitals and one central private laboratory), Iran, over nine months from December 2021 to July 2022, were collected. All bacterial isolates were confirmed for *A. baumannii* using biochemical tests, including Gram-staining, TSI, Urease, Oxidase, SIM, MRVP, Simon citrate, ONPG, and Dnase [14].

Antibiotic susceptibility test

The antibiotic susceptibility test followed the Kirby-Bauer protocol according to the Clinical and Laboratory Standards Institute (CLSI) [15]. Administrated antibiotics were included cefepime (30 µg), ampicillin sulbactam (20 µg), cotrimoxazole (1.25/23.75 µg), amikacin (30 µg), ceftazidime (30 µg), meropenem (10 µg), gentamicin (10 µg), ciprofloxacin (5 µg), colistin (10 µg), cefotaxime (30 µg), and piperacillin tazobactam (10/100 µg) (Padtan-Teb, Iran [16](.

Minimum inhibitory concentration (MIC)

Colistin MIC was evaluated through colistin broth disk elution (CBDE) with 1, 2, and 4 µg/mL concentrations [15]. Carbapenem resistance test via MIC was conducted using Etest containing meropenem. MIC≤2 µg/mL was considered intermediate resistance, and MIC≥4 µg/mL was resistant. All tests were performed in triplicate to ensure reproducibility of results [15].

Phenotypic investigate of resistance to Carbapenem

Since metallo-β-lactamase enzymes are inhibited by dipicolinic acid (DPA) and EDTA, the combined disc method employed a combination test of DPA and meropenem. The zone of growth inhibition around the combined disc of meropenem and this compound was compared with the zone around the meropenem disc alone. An increase in the diameter of the inhibition zone by more than 5 mm with the combined discs compared to meropenem alone indicates the presence of metallo-β-lactamase enzymes [15].

Carbapenemase Gene identification

Genomic DNA from *A. baumannii* isolates was extracted using a simple boiling method, as described previously [17]. To evaluate the presence of carbapenemase genes (bla_{VIM}, bla_{NDM}, and bla_{IMP}), the polymerase chain reaction (PCR) test was performed with final reaction volume of 25 µl Master Mix RED (Ampliqon, Denmark), and designed primers (Table 1S1). PCR was evaluated using the following cycling conditions: one cycle for initial denaturation at 94 °C for 10 min, followed by 36 cycles consisting of denaturation at 94 °C for 30 s, annealing at 52 °C for 40 s, and extension at 72 °C for 50 s; and finally, one cycle for the final extension at 72 °C for 5 min. The

presence of bla_{OXA51}, bla_{OXA-23}, and bla_{OXA-58} genes was evaluated using the following cycling conditions: one cycle for initial denaturation at 94 °C for 5 min, followed by 30 cycles consisting of denaturation at 94 °C for 25 s, annealing at 52 °C for 40 s, and extension at 72 °C for 50 s; and finally, one cycle for the final extension at 72 °C for 6 min [7].

Multilocus sequence typing (Mlst)

MLST was conducted to evaluate the two colistin-resistant isolates in accordance with the Pasteur scheme. This involved the amplification of seven housekeeping genes: *fusA*, *gltA*, *pyrG*, *recA*, *cpn60*, *rplB*, and *rpoB*, as detailed on the MLST website (http://pubmlst.org/abaumannii/), which provides information on PCR conditions and primers. The allelic numbers and sequence types (STs) for each strain were established by comparing their nucleotide sequences against the *A. baumannii* PubMLST database [13].

Genes sequencing

After the PCR test, the selected genes were sent to Pishgaman Biotech company for sequencing and were registered at the NCBI database.

Statistical analysis

Data were reported by number, percentages, and mean±standard division (SD).

Results

Bacterial isolation and identification

Of 100 clinical samples from hospitalized patients, 60 isolates from 23 (38.4%) females and 37 (61.6%) males were diagnosed with *A. baumannii*, which 20 (33.3%) isolates were obtained from bloodstream, 10 (16.6%) from wounds, 7 (11.6%) from urine samples, 5 (8.3%) from tracheal samples, 4 (6.6%) from respiratory samples, 2 (3.3%) from sputum samples, and 2 (3.3%) from CSF. Additionally, 2 (3.3%) isolates were obtained from secretion samples, while one isolate from each bronchial (1.6%), pleural (1.6%), and throat (1.6%) samples were collected.

Antibiotic resistance pattern

The results of antibiotic susceptibility testing for *A. baumannii* isolates reveal high rates of resistance to several antibiotics. Broad-spectrum cephalosporins, including cefepime (98.3%), ceftazidime (100%), and cefotaxime (100%), exhibited resistance. Aminoglycosides, such as amikacin (96.7%) and gentamicin (95.0%), also demonstrated limited effectiveness against the isolates, with the majority showing resistance. Similarly, fluoroquinolones like ciprofloxacin exhibited complete resistance (100%). However, polymyxins, particularly colistin, showed notable efficacy, with the most sensitive isolates (96.7%). Beta-lactam combination agents, such as piperacillin-tazobactam and ampicillin-sulbactam, displayed limited effectiveness, with most isolates showing resistance (100%). Trimethoprim-sulfamethoxazole demonstrated moderate sensitivity (3.3%). Carbapenem, represented by meropenem, showed complete resistance across all isolates (100%) (Table 1).

MIC results

Among the 60 carbapenem-resistant *A. baumannii* strains, 2 strains (3.3%) had turbidity at a 4 µg/ml MIC that were considered resistant to colistin. No turbidity was observed for 58 strains (96/6%) at MICs of 1 µg/ml, 2 µg/ml, and 4 µg/ml. Therefore, MIC was 1 µg/ml, indicating isolates were sensitive to colistin.

Antibiotic resistant genes

Based on the antibiotic resistance pattern, 25 isolates were chosen for PCR analysis targeting bla_{OXA-51}, bla_{OXA-23}, bla_{OXA-58}, bla_{NDM}, bla_{IMP}, and bla_{VIM} genes. PCR results revealed that among the selected isolates, 15 (60.0%) harbored the bla_{OXA-23} gene, 23 (92.0%) contained the $bla_{OXA-51\ gene}$, and 1 (4.0%) isolate carried the

Table 1 Antibiotic susceptibility results for *Acinetobacter Baumanni* isolates

Antibiotics		Sensitive %	Intermediate %	Resistance %
Broad-spectrum cephalosporins	(FEP) Cephepim	1 (1.7)	0 (0.0)	59 (98.3)
	(CAZ) Ceftazidime	0 (0.0)	0 (0.0)	60 (100)
	(CTX) Cefotaxime	0 (0.0)	0 (0.0)	60 (100)
Aminoglycosides	(AN) Amikacin	2 (3.3)	0 (0.0)	58 (96.7)
	(GM) Gentamicin	3 (5.0)	0 (0.0)	57 (95.0)
Fluoroquinolones	(CIP) Ciprofloxacin	0 (0.0)	0 (0.0)	60 (100)
Polymyxins	(CL) Colistin	58 (96.7)	0 (0.0)	2 (3.3)
B-Lactam Combination Agents	(TZP) Piperacillin-tazobactam	0 (0.0)	0 (0.0)	60 (100)
	(SAM) Ampicillin- sulbactam	1 (1.7)	0 (0.0)	59 (98.3)
Folate pathway inhibitors	(SXT) Trimethoprim-sulfamethoxazole	2 (3.3)	0 (0.0)	58 (96.7)
Carbapenem	(MEM) Meropenem	0 (0.0)	0 (0.0)	60 (100)

Table 2 Charecterization of two colistin resistant *A. baumannii* isolates according to MLST profile, clinical sample and antibiotic resistant pattern

Isolate	ST	CC	Clinical sample	Antibiotic resistant pattern	
1	2	CC2	Urine	FEP, CAZ, CTX, AN, GM, CIP, CL, TZP, SAM, SXT, MEM	*bla-OXA23*, *bla-OXA51*, *blaNDM*
2	2	CC2	Tracheal	FEP, CAZ, CTX, AN, GM, CIP, CL, TZP, SAM, SXT, MEM	*bla-OXA23*, *bla-OXA51*,

(FEP) Cephepim; (CAZ) Ceftazidime; (CTX) Cefotaxime; (AN) Amikacin; (GM) Gentamicin; (CIP) Ciprofloxacin; (CL) Colistin; (TZP) Piperacillin-tazobactam; (SAM) Ampicillin- sulbactam; (SXT) Trimethoprim-sulfamethoxazole; (MEM) Meropenem

bla_{NDM} gene. Also, $bla_{IMP,}bla_{VIM}$ and bla_{OXA-58} genes were not detected.

MLST analysis

MLST analysis of colistin-resistant isolates identified that the two isolates were assigned to ST2. Overall, using the goeBURST algorithm, STs were belonged to one CCs including CC2(ST2) (Table 2).

Genes sequencing

Three bla_{OXA-51}, bla_{OXA-23}, and bla_{NDM} genes from five isolates after the PCR test were sequenced and were deposited in the NCBI database with the accession numbers LC723919, LC723916, LC723917, LC723918, and LC723920 (Table 2S1).

Discussion

In this study, *A. baumannii* strains were commonly isolated from males, wound specimens, urine, bloodstream, and respiratory secretions. Akbarpour et al. reported that among 248 isolates of *A. baumannii*, all were MDR and isolated from the upper respiratory tract. In contrast, the urinary tract exhibited the lowest prevalence of *A. baumannii*. They reported that the highest contamination rate occurred in males and patients in the ICU [18]. In another study, Gharaibeh et al. found a high prevalence of MDR *A. baumannii* isolates among ICU patients [19]. Furthermore, significant risk factors associated with a poor prognosis in *A. baumannii* bacteremia encompass underlying medical conditions, pneumonia as the source of bacteremia, surgical procedures, invasive operations, mechanical ventilation, ICU stay, and length of hospitalization.

Most studies isolated *A. baumannii* strains from respiratory samples [20, 21]. The prevalence of tracheal infections was higher than other respiratory samples in the current study. Similarly, Bardbari et al. reported that *A. baumannii* strains isolated from tracheal aspirate specimens were the most common respiratory isolates [22]. Most of the *A. baumannii* strains isolated from our samples were from the bloodstream.

We observed the highest resistance to broad-spectrum cephalosporins and colistin sensitivity. Colistin, or polymyxin E, is an antibiotic used as a last-line treatment for MDR Gram-negative infections, including pneumonia. Lupo et al. demonstrated that *A. baumannii* and *Pseudomonas aeruginosa* (*P. aeruginosa*) could both acquire multiple resistance beta-lactamases or carbapenemases [23].

Another study illustrated that all *A. baumannii* isolates were MDR, and minocycline and tigecycline were the most effective drugs against *A. baumannii* [24]. The primary cause of carbapenem resistance typically involves either a decrease in drug accumulation levels or an elevation in the expression levels of efflux pumps [25, 26]. The utilization of colistin for *A. baumannii* infections has resulted in the emergence of resistant bacterial strains. These strains have also acquired resistance to antimicrobial compounds naturally produced by the human immune system [27, 28]. In the current study, 60.0% harbored the bla_{OXA-23} gene, 92.0% contained the bla_{OXA-51} gene, and 4.0% isolate carried the bla_{NDM} gene, while we did not find any isolated with $bla_{IMP,}bla_{VIM}$ and bla_{OXA-58} genes. The $bla_{OXA-51-like}$ genes have been reported to be present in *A. baumannii* chromosomes [29].

Jiang et al. found that most carbapenemase-resistant genes bla_{OXA-23}, bla_{TEM-1}, and bla_{OXA-66} were detected the most *A. baumannii* every year from 2008 to 2019 [30]. Feizabadi et al. demonstrated a broad range of bla_{OXA} genes present among *A. baumannii* strains in Iran and reported that identifying *bla*(*OXA-51*-like) can serve as a straightforward and dependable means to distinguish *A. baumannii* strains from other species [31]. Another study by Leungtongkam et al. showed that bla_{IMP} and bla_{VIM} genes were not found among *A. baumannii* isolates, while bla_{NDM-1} was detected in some isolates and only one isolate expressed bla_{OXA-23}-bla_{OXA-58}-bla_{NDM-1} [32]. The main contributor to carbapenem-resistant *A. baumannii* is regarded as carbapenemase production, particularly by *OXA* genes, *notably* bla_{OXA-23} [32].

The escalating resistance of clinical strains of *A. baumannii* to antibiotics presents a significant challenge in healthcare settings. These resilient strains, characterized by their rapid proliferation, exacerbate the complex landscape of infection treatment. Consequently, the efficacy of various antibiotic treatments is compromised, resulting in prolonged illnesses, heightened healthcare costs, and increased mortality rates. The advent of nanotechnology has led to a substantial rise in the application of nanoparticles (NPs) across diverse domains, including the management of antimicrobial resistance [33, 34].

ST2 was assigned to two colistin-resistant *A. baumannii* isolates based on the MLST analysis. The ST2 clone,

which represents the predominant sequence type within the CC2 or international clone two, has been identified as the most widespread sequence type in several countries, including Italy, Greece, Turkey, Lebanon, and Algeria, according to data from Iran [9, 35–40].

Although various ST clones have been identified in Iran, recent studies by Piran et al., Hojabri et al., Rezaei et al., and Hajihashemi et al. indicate that the ST2 clone is currently the most prevalent. Additionally, ST2 has been widely distributed in clinical settings among Iranian patients, representing approximately 62–90% of isolates [9, 39–41].

Conclusion

A. baumannii isolates demonstrated high resistance to multiple antibiotics commonly used in clinical practice, including broad-spectrum cephalosporins, aminoglycosides, fluoroquinolones, and carbapenems. However, colistin showed notable efficacy against the majority of isolates. We identified the presence of carbapenemase-producing strains, particularly those harboring the bla_{OXA-23} gene, indicating the importance of vigilant monitoring and infection control measures to combat the spread of MDR *A. baumannii* infections in hospital settings.

The MLST analysis indicates colistin-resistant isolates belonged to ST2 and is endemic in Iran.

Limitations

While we comprehensively investigated the genes associated with carbapenemase genes among clinical isolates, our study had limitations in sample size and the rigorous methodology employed, which may limit the generalizability of our findings to broader populations or geographical regions.

Abbreviations

MDR	Multidrug-resistant
MLST	Multilocus Sequence Typing
RAPD	Random Amplification of Polymorphic DNA
STs	Sequence types
CSF	Cerebrospinal fluid
CBDE	Colistin broth disk elution
DPA	Dipicolinic acid
PCR	Polymerase chain reaction
SD	Standard division

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13104-024-07047-5.

Supplementary Material 1

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Author contributions

Conceived and designed the experiments: KSN, DSh, and SGh, Performed the experiments: KSN, YA and SGh, performed statistical and spatial analyses and interpreted all the results. KSN, DSh, and SGh, contributed to the writing of the manuscript and revised the final version manuscript: KSN, YA and SGh. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of Babol University of Medical Sciences; Babol, Iran. However, consent to participate was waived by Research Ethics Committee of Shahid Ashrafi Esfahani University, Isfahan, Iran, due to bacteria isolated from clinical samples in the clinical microbiology laboratory routinely.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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